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Semin Oncol. 1992 Dec;19(6):639-45.

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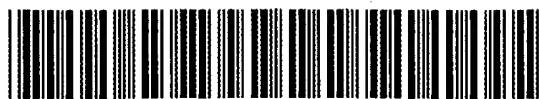
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## Advances in vinca-alkaloids : Navelbine®

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**Abstract.** Vinorelbine (Navelbine®) is a new semi-synthetic vinca alkaloid which chemically differs from vinblastine by substitutions on the catharanthine moiety of the molecule. It has shown promising experimental antitumor activity against experimental murine tumors as well as continuous cell lines of human neoplastic origin and human tumor xenografts in nude mice. Acute subacute and chronic toxicity extensively studied in rodents, dogs and primate has shown that hematotoxicity was almost the sole side-effect; neurotoxicity appears very limited. Almost exclusive affinity of NVB for mitotic tubulin and tubulin associated protein accounts for this pattern of toxicity. Phase I and II studies have been conducted in humans. Dose limiting side-effect appears to be neutropenia: the drug is slightly emetogenic, induces little alopecia, almost no neurotoxicity, and no other toxicity. Although preliminary, results of phase II studies already suggest significant activity of NVB in non small lung cancer (33% response rate in 78 evaluable patients), advanced breast cancer (53% response rate in 33 pts without significant chemotherapy for the target progression) and Hodgkin's disease (90% response rate after 4 weekly courses in 31 pts). Thus extensive pharmacological studies and ongoing clinical studies confirm that chemical modifications of the catharanthine moiety of vinca alkaloid can lead to active agents with broader spectrum of activity and easily manageable side effects.

catharanthine. Elle possède une activité antitumorale expérimentale intéressante à l'égard des leucémies et tumeurs murines, de lignées cellulaires tumorales d'origine humaine et de xénogreffes tumorales chez la souris athymique. Ses toxicités aiguës, subaiguës et chroniques, extensivement étudiées chez le rongeur, le chien et le singe, se limitent pratiquement à la neutropénie; en particulier, la neurotoxicité est très minime. Son affinité presque exclusive pour la tubuline et le complexe tubuline-proteïnes associées microtubulaires du fuseau mitotique rend bien compte de cette toxicologie. Les études cliniques précoces de phase I et II sont engagées. La neutropénie est la toxicité dose-limitante; la molécule est faiblement émetogène, très peu alopeciante et pratiquement non neurotoxique. Les résultats de phase II déjà obtenus suggèrent une activité très significative dans les cancers bronchiques non micro-cellulaires (33 % de réponses chez 78 malades), les cancers du sein métastatiques (53 % de réponses chez 33 malades sans traitement significatif de l'évolution métastatique) et la maladie de Hodgkin (90 % de réponses après 4 cycles hebdomadaires de traitement chez 31 malades). Une étude pharmacologique exhaustive et les études cliniques en cours confirment que les modifications du noyau vindoline des vinca-alkaloïdes permettent l'obtention d'agents à spectre et niveau d'activité importants et à toxicité réduite.

**Key words :** Vinca-alkaloids — Navelbine®

### Actualités sur les vinca-alkaloïdes : la Navelbine®

**Résumé.** La vinorelbine (Navelbine®) est un vinca-alkaloïde semi-synthétique qui diffère de la vinblastine par l'introduction d'une double liaison dans le noyau

Since the original observation of antileukemic effect of vinca-alkaloïds (VA) in mice, [9] this class of agents has originated intense research work leading to the identification and use of vincristine (VCR) and vinblastine (VLB) as anticancer agents. Vindesine (VDS), a semi-

synthetic VA has been studied since 1975 [17] : whether or not this compound has brought a significant improvement over the former VA in terms of spectrum of activity and/or tolerance remains unclear. Simultaneously, mechanisms of action, pharmacokinetics, mechanisms of resistance have received meaningful attention.

Those 3 molecules chemically differ by substitutions on the vindoline moiety of the molecule. An original synthesis process, using a modified Polonowski's reaction with Nbeatharantine oxide allowed the production of anhydrovinblastine and thus of nor-5'- derivatives [7]. Among these, nor-5'-anhydrovinblastine has shown promising experimental antitumor activity leading to extensive preclinical and clinical studies : these studies have confirmed the peculiar properties of the molecule and its clinical studies. Since most of the published material refer to nor-5'-anhydrovinblastine as navelbine instead of INN vinorelbine, we shall use this denomination and the NVB abbreviation in this review.

### Chemical and physical data

#### Structural formula

The formula of NVB (3',4'-didehydro-4'-deoxy-C'-norvincaleucoblastine) as well as major differences with other VA are shown in Fig. 1. It should be emphasized that these differences affect the cathartantine moiety of the molecule.

#### Physical properties

Molecular weight of the ditartrate salt is 1079.15; it is a yellow white amorphous powder; the molecule is soluble in water and ethanol; it is formulated as a ready to use saline solution of vinorelbine ditartrate (10 mg/ml of NVB).

#### Experimental antitumor activity

Experimental antitumor activity has been studied in a number of models both in vitro and in vivo. Whenever data concerning other VA with similar models are available, they are described to allow for comparison.

#### In vitro antitumor activity

Antitumor activity of NVB has been studied on more than 30 malignant cell lines. In all cases but one (breast cancer cell line resistant to doxorubicine), IC<sub>50</sub> are in the range of 10<sup>-9</sup> to 10<sup>-7</sup>M : such concentrations are readily achieved in man using a dose of 30 mg/m<sup>2</sup>. When compared to that of other VA (L1210 leukemia, ovarian carcinoma A2780, breast cancer) activity is close to the one observed with the most active VA. If doses used in vivo in man are taken into account, the therapeutic index could be 10 to 40 times that of other VA. NVB ranked second on the NSCLCNGL2 cell line (derived from non small cell lung carcinoma).

Results observed with cell-lines resistant to doxorubicin (L1210, A2780) suggest that pleiotropic drug resistance phenotype (PDR) strongly affects NVB activity.

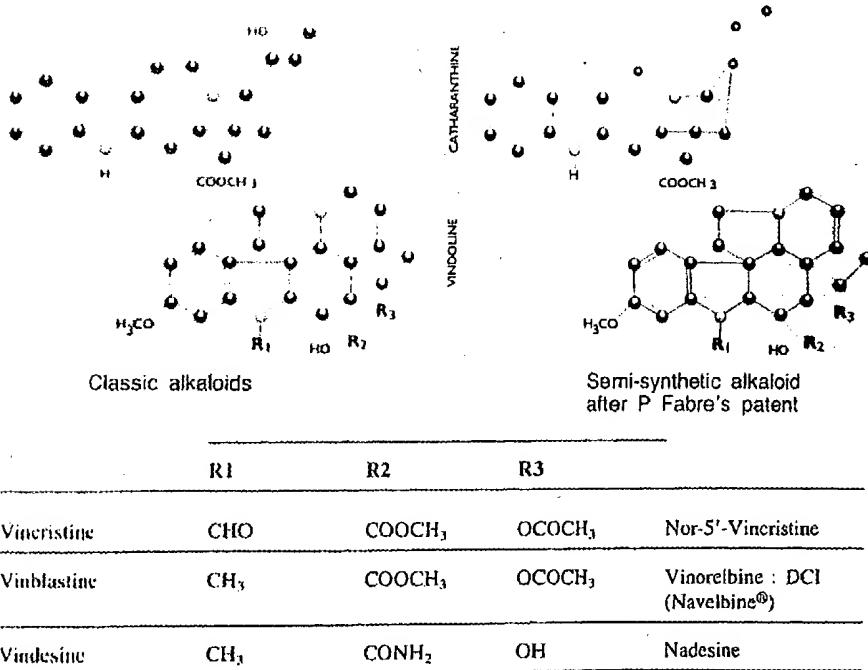


Fig. 1. Vinca-alkaloid

**Table 1.** Activity of vinorelbine on murine tumors grafted in mice

Tumor/route	Schedule	Optimal T/C (%)			Conclusion
		NVB	VCR	VLB	
P388/IV	IV, D1	>253	152	176	Active
P388/IP	IV, D1	>278	168	193	Active
P388/SC	IV, D1, 7, 13	>200	>200	>200	Active
P388MDR/IP	IV, D1	<120	NA	<120	Inactive
L1210/IP	IV, D1	184	NA	NA	Active
B16/SC	IP, D1-9	168	103	145	Active

### *In vivo antitumor activity*

Antitumor activity of NVB has been studied on tumors grafted in mice. Main results are depicted in Table 1. Those results achieved with both the tumor and NVB being administered by IP route are not shown.

NVB shows significant activity against P388 leukemia (the only VA to induce a significant cure rate), L1210 leukemia and, the B16 melanoma.

While IV route appears optimal, a significant activity is achieved by oral route (data not shown).

Its activity is slightly dependant upon schedule with better results achieved with weekly administration.

NVB retains some activity against a P388 subline resistant to VCR.

NVB, given as a single IV dose has demonstrated activity against 5 human tumor xenografts in nude mouse : LX-1 and QG-56 (lung, squamous carcinoma), QG-36 (lung, small cell carcinoma), MX-1 (breast cancer) and 04-1-ST (gastric, adenocarcinoma).

### Toxicology studies

General as well as specific studies directed towards neurotoxicity have been extensive.

#### *Acute toxicity*

LD10 is achieved, depending upon the species studied following a single dose of .7 (dog) to 60 mg/m<sup>2</sup> (rodents). In those animals : dog appears the most sensitive species, a common finding with VA; the dose-limiting toxicity is the hematological one; when compared to other VA, NVB LD10 is 3 to 15 times higher.

#### *Subacute and chronic toxicity*

Subacute and chronic toxicities of NVB have been studied in rats, dogs, rhesus monkeys using weekly administration, biweekly administration, IV administration for 5 consecutive days every 3 weeks. Following parameters have been studied : lethal dose, clinical

**Table 2.** Subacute and chronic toxicity of NVB

	Rats	Dogs	Rhesus monkeys
MTD (mg/kg/w)	2	0,75	2
Duration (weeks)	9	12	36
neutropenia	100%	100%	100%
anemia	>3 weeks	mild	mild
thrombocytopenia	none	none	none
LFT (transaminases)	>60%	>60%	none
Cardiovascular	none	none	none
Respiratory	none	none	none
Neurotoxicity	none	none	none

condition, blood cell counts, electrolytes, liver function tests, neurotoxicity and pathology (Table 2) :

- dogs are here again the most sensitive animal : maximum tolerated weekly doses are 2 mg/kg in rats, 2 mg/kg in monkey and 0.75 mg/kg in dogs;

- administration for 5 consecutive days every 3 weeks in monkeys compares favorably in terms of dose-intensity to weekly dosing;

- myelosuppression is the main toxicity : it is manifested predominantly by a non cumulative reversible neutropenia. Mild anemia appears after repeated doses. No thrombocytopenia is observed;

- hepatotoxicity manifested by reversible cytolysis is observed in rats and dogs but not in monkeys;

- no neurotoxicity has been observed : it was studied in monkeys, an animal specifically sensitive to VA neurotoxicity, using not only clinical examination but also pathological studies with specific myelin characterization, looking for axon and myelin degeneration and ensuing degeneration of striated muscles [18] : in those models neurotoxicity of VCR and VDS have been readily characterized [3];

- no modification of cardio-vascular or respiratory parameters has been observed;

- spermatogenesis is unaffected in monkeys.

### Mutagenesis

As described with other VA, NVB is mutagenic in the chromosomal mutations tests (micronucleus test, Sister Chromatid Exchange) but is not responsible for gene mutation (Ame's test, LS178YTK+/-).

### Teratogenesis

In mouse and rabbit, NVB is embryotoxic but no teratogenesis is observed.

### Pharmacokinetics, cellular pharmacology, mechanism of action

Pharmacokinetics, cellular pharmacology and mechanism of action of NVB have deserved extensive studies which have brought insight on structure-activity relationship with VA and peculiar activity/toxicity of NVB.

### Pharmacokinetics

Pharmacokinetics have been studied in animals and humans either using radio-labelled, NVB, or a sensitive and specific radio-immuno-assay [14]. While large interspecies variations are observed, studies in primate and humans have demonstrated similar pharmacokinetic parameters.

**Plasma elimination curves.** Main pharmacokinetic parameters in rat, primate and human [15] and comparison with those reported for other VA [3, 11, 16] are depicted in Table 3.

In all species plasma decay of NVB follows a bi- or triphasic pattern : while there is good agreement at early times between RIA and measure of radioactivity, the discrepancies after 24 suggest that metabolites account then for the majority of radioactive material. Lower Cmax, shorter terminal half-life and higher clearance are noticed in rats as compared to human; pharmacokinetics in primate are similar to that in human.

High protein binding (80%) is observed at early times and decreases thereafter.

In most of the patients a dose and/or time dependence was evidenced.

**Table 3.** Comparative pharmacokinetics of vinorelbine in rats, monkeys and humans. NVB was measured using RIA following a single IV bolus injection

	Rats (Wistar)	M. Rhesus	Humans
Tmax	5 min	3 min	5 min
Plasma decay	triphasic	triphasic	bi/triphasic
AUC (ng/ml/h)	447	1971	2250
Clairance (l/h/kg)	2.2	0.53	0.41
Terminal T1/2 (h)	10	35	22-68

When compared to other VA, pharmacokinetics of NVB does not show striking differences. The correlation suggested by previous studies between the terminal half-life and the maximum weekly dose tolerated in human [12], does not stand true with NVB (Table 4).

Thus pharmacokinetics of NVB cannot account for peculiar toxicity/activity spectrum.

**Elimination.** Elimination of radiolabelled NVB has been studied in mouse, rat, primate and humans : less than 12% are found in urine within 72 h following IV bolus administration; 50-70% of radioactivity are eliminated in the feces. However in primates and humans less than 20% of radioactivity are recovered in the feces in the 48 h following injection.

Thus no dose-modification is warranted in case of renal failure while dose adjustment can be needed in case of cholestasis.

**Metabolism.** As pharmacokinetics had demonstrated that metabolism of NVB (and other VA) occurred, this metabolic pathway has deserved specific studies.

• **Perfusion of isolated rat liver.** Those studies with 3H-NVB have shown : that NVB is responsible for a transient decrease of biliary output; that intense hepatic extraction did occur with less than 60% of the infused dose recovered in the effluent in 2 h; active biliary excretion with bile concentrations 1000 to 7000 fold higher than in the effluent; with hepatic metabolism : 3 metabolites account for 60% of bile radioactivity, although they are not found in the effluent.

**Table 4.** Pharmacokinetics of vinca alkaloids in human values are expressed when data are available as mean (+SD)

Parameter	Vincristine	Vinblastine	Vindesine	Navelbine
T1/2 alpha	2.6 min	2.6 min	1.3 min	2.6 min
T1/2 beta (h)	2.27 (1.50)	1.64 (0.34)	0.912 (0.373)	1.9 (0.8)
T1/2 gamma (h)	85 (69)	24.8 (7.5)	24.2 (10)	40 (18)
Vss (l/kg)	8.42 (3.17)	27.3 (15)	8.84 (4.35)	27 (19)
Clearance (l/kg/h)	0.106	0.252	0.740	0.8 (0.53)
Urinary elimination	10-20%	<10%	<10%	<8%

- *Short term incubation with viable human hepatocytes.* Human viable hepatocytes maintained in suspension are exposed to  $5 \cdot 10^{-7}$  M 3H-NVB.

Influx is intense and rapid with 55% of radioactivity entering the cellular fraction in 1 min, and 80% after 1 h. While unchanged NVB accounts for 90% of intracellular radio-activity after 2 h, 72% of extracellular radio-activity are accounted for by 2 ou 3 metabolites.

- *Identification of metabolites.* Preliminary observations suggest that Navelbine-N-oxide is one of the metabolites and deacetyl-navelbine a second one.

#### Tissue distribution

Tissue distribution of vinorelbine has been studied in mouse, rat and primate.

As for all VA, NVB undergoes intense tissue fixation with the highest concentrations found in spleen, liver, kidney, heart. High tissue levels are also found in the lungs.

With quantitative determinations, tissue concentrations are 3 to 10 times higher than with other VA. This tissue distribution account for higher distribution volume of NVB.

#### Binding and influx

Rapid and intense intracellular influx is observed with Navelbine : 2 binding sites can be characterized on plasma membranes (a) high affinity binding site ( $K_d = .104 \mu M$ ), (b) low affinity binding site ( $K_d = 59.2 \mu M$ ); passive transport ( $K_m = 2.38 \mu M$ ) accounts for 35% of influx; active, energy requiring transport accounts for 25% of influx.

#### Mechanism of action

Main mechanism of action of VA is their binding to tubulin resulting in their action on the assembly/diassembly of microtubules [3, 8, 11]. Microtubules are involved in the structure of cytoskeleton, the migration of chromosomes during mitosis, the neuronal axoplasmatic transport. Tubulin — the smallest unit of microtubules — is an ubiquitous dimeric protein (molecular weight 110,000). It possesses 2 binding sites for VA [2], as well as different binding sites for GTP and GDP [19], colchicine and podophyllotoxine : the low affinity site appears involved in the inhibition of tubulin polymerization while the high affinity site seems to be connected with formation of paracrystals. A direct relation exists between VA induced inhibition of tubulin polymerization, potency for arresting mitosis and experimental antitumor activity [13], so that inhibition of tubulin polymerization has became a screening test for the search of cytotoxic VA. Differences in the tubulin associated proteins and specifically in TAU content

between axonal and other tubulin-high TAU content accounting for VA induced tubulin spiraling—can explain peculiar neurotoxicity of some VA (VCR, VDS).

*Effect on cell cycle.* It has been studied on L1210 cells grown exponentially using flow cytofluorometry. NVB is a phase specific agent, with qualitative and quantitative effects similar to that of VCR; after cell exposure to non cytotoxic concentrations, no modifications of cell cycle are observed (10 nM); when cytotoxic concentrations are used ( $>12 \text{ nM}$ ), a block in G2-M phases is induced, with subsequent cell death during interphase or second mitosis (at high NVB concentrations).

*Inhibition of microtubules assembly.* Inhibition of microtubules assembly has been studied using both the microtubules complex (tubulin, MAPS), and in vitro reconstituted system with purified tubulin and homologous or heterologous associated proteins. As shown in Table 5, vinorelbine, vincristine and vinblastin have a very similar effect, vincristine being slightly more active.

Table 5. Inhibition of tubulin polymerization in reconstituted system with purified adult (A) or newborn (N) rat tubulin and TAU. ID50 = concentration of drug required to block polymerization of tubulin by 50%

	ID50 ( $\mu M$ )		
	VCR	VLB	NVB
Tubulin A + TAU A	0.7	1	0.9
Tubulin A + TAU N	0.2	0.3	0.4
Tubulin N + TAU N	0.2	0.3	0.4

*Induction of tubulin spiraling.* To induce spiraling, much higher concentrations of NVB are required (2.5 to 4 times) than with VCR. Thus NVB appears as active as other VA when the cytotoxic mechanism is studied, while the low spiraling potency suggests sparing of axons and better therapeutic index.

*Action on different types of microtubules.* It has been studied on 11 days mice embryos, using immunocytochemistry. Table 6 summarizes data from those studies. If VCR is the most active VA it affects 3 types of microtubules within the same range of concentrations. NVB is almost as active as VCR on mitotic microtubules and requires concentrations similar to those of VLB to affect axonal microtubules.

#### Early clinical studies with Navelbine

Preclinical studies with vinorelbine demonstrated promising characteristics, therapeutic index and warranted clinical studies in humans.

**Table 6.** Effect of VA on various microtubular types in mouse embryo. Concentrations ( $\mu\text{M}$ ) achieving depolymerization after 90 min incubations are shown

Agent	Microtubular types			
	Mitotic		Inter phasic Axonal	
	Kineto choriae	Inter polar		
Vincristine	2	2	5	5
Vinblastine	40	2	5	30
Vinorelbine	5	2	5	40

### Phase I study

Thirty-four patients with various malignancies refractory to conventional therapy entered this phase I study. NVB was given as a short weekly intra-venous infusion, with a starting dose of  $3 \text{ mg/m}^2$ . Further doses were defined according to a modified Fibonacci scheme, up to level 6 ( $36 \text{ mg/m}^2$ ). 29/34 patients had previously received VA.

Clinical tolerance has been excellent : 1 patient experienced grade 1 nausea and vomiting; no evaluable patient had alopecia; peripheral neuropathy was observed in 1 patient; 3 patients experienced grade 1 skin rash; 2 patients had grade 1 constipation.

Grade 1 increment in transaminases occurred in 1 patient.

Leuco-neutropenia was the dose limiting side effect : leucocyte nadir ranged from  $2.6 \text{ g/l}$  to  $5.2$  depending upon the dose ( $27$  and  $36 \text{ mg/m}^2$ ) and the number of drug administrations. 2/18 patients receiving a dose of  $27 \text{ mg/m}^2$  had thrombocytopenia (4/91 cycles).

The dose recommended for further studies was  $30 \text{ mg/m}^2$ .

Although response rate was not an aim of this study, 2/16 patients with lymphomas experienced a partial response.

### Phase II studies with Navelbine

Subsequently disease oriented phase II studies have been initiated. A weekly IV dose of  $30 \text{ mg/m}^2$  was scheduled in all the phase II studies. This review will focus first on activity then on tolerance pooling the data from all the phase II studies.

#### Phase II study in Non Small Cell Lung Cancer.

Activity of navelbine against lung cancer derived cell lines, as well as distribution of the drug in the lungs have prompted phase II studies in Non Small Cell Lung Cancer (NSCLC).

To be eligible patients should have pathologically confirmed NSCLC, without prior chemotherapy, not amenable to surgery and/or radiotherapy.

NVB was administered IV at a weekly dose of  $30 \text{ mg/m}^2$  until progression or severe toxicity. Response was evaluated after 8 cycles (2 months).

Seventy eight patients fulfilling eligibility criteria received 981 cycles with a mean dose of  $29.3 \text{ mg/m}^2$ . Seventy-eight are evaluable for tolerance, 69 are evaluable for response. Twenty-three experienced at least partial response ( $33\% \pm 11\%$ ) (Table 7).

**Table 7.** Responses in the phase II study of navelbine in non small cell lung cancer according to stage and pathology

Stage	I (n=7)	II (n=1)	III (n=22)	IV (n=39)	All patients (n=69)
Squamous cell (n=49)	5	—	6	6	17 (34,7%)
Adenocarcinoma (n=15)	—	—	1	2	3 (20%)
Undifferentiated (n=5)	—	—	1	2	3 (60%)
	5 (71%)	—	8 (36,4%)	10 (25,6%)	23 (33,3%)

Median survival of the treated population was 32 weeks; median survival time of responders is 63 weeks. Median duration of response has been 34 weeks. In 8 patients response has lasted for more than 12 months [5].

Thus with a response rate of 33 %, navelbine appears one of the most active single agent in the chemotherapy of Non Small Lung Cancer [10]. The tolerability of weekly injections has permitted maintenance therapy in the responders, which can in part account for the duration of responses.

Tolerance will be analyzed for all the patients treated during the phase II trials. Nevertheless, hematological tolerance in the NSCLC trial is of specific interest because of the duration of therapy in some patients.

Leucopenia and neutropenia have been the most significant side effect : neutropenia was observed in 49 % of cycles, graded (WHO) 3-4 in 21.4 % of cycles. However it was non cumulative, and of short duration (<7 days).

Anemia was observed in 42 % of cycles (40 % G1-2). No episode of thrombocytopenia was observed.

**Phase II study in advanced breast cancer.** Thirty-six patients with advanced breast cancer entered the first study. Fourteen had previously received adjuvant chemotherapy; 10 had received chemotherapy as treatment of metastatic evolution; 13 had previously received hormonal therapy. Dominant sites of disease was : visceral [14], bone [14], soft tissue [12]. Navelbine was

given weekly at a dose of 30 mg/m<sup>2</sup> as a short IV infusion until progression or severe toxicity. Thirty-two pts are evaluable for response (438 cycles). Objective responses (PR+CR) have been achieved in 17 patients (53%±17%) with 4 of them achieving complete response, 2/7 treated with palliative chemotherapy experienced a partial response. Although preliminary, these results [4] suggest a striking activity in advanced breast cancer; ongoing studies should help to define more precisely the level of activity.

*Phase II study in advanced ovarian carcinoma.*

Thirty-four patients with advanced ovarian carcinoma were treated according to the same schedule. All had previously received cisplatin containing chemotherapy and 9 had received pelvic or pelvic and abdominal irradiation.

In those heavily pretreated patients neutropenia was more pronounced (grade >=3 in 27% of cycles); thrombocytopenia occurred in 2 patients and 3 cycles.

One CR and 4 PR were achieved in 32 evaluable patients for a response rate of 15% [18].

Further studies are needed to assess activity of navelbine as second line therapy in patients previously treated with organo-platinum containing regimens.

*Phase II study in Hodgkin's disease.* It has been possible to conduct a phase II study with navelbine in patients with advanced previously untreated Hodgkin's disease, as emergency treatment and before those patients could be given conventional chemotherapy (MOPP-ABVD). Thirty-two patients received 125 cycles of navelbine. Twenty-two had stage III or IV disease. In those young previously untreated patients, hematological side effects were reduced : neutropenia was observed in 17% of cycles.

After 4 weeks of navelbine therapy, 28/31 patients (90%) had experienced at least partial response.

This study suggests a striking activity of navelbine in Hodgkin's disease. Trials are now in progress aiming at the study of navelbine containing regimens in second line therapy in patients with Hodgkin's disease.

*Tolerance during phase II studies.* Side effects have been compiled throughout 1789 navelbine administrations during the phase II studies.

- *Hematological side effects.* Neutropenia is the main side effect : significant neutropenia (grade >2) has been observed in 23% of cycles. It is reversible and of short duration (<7 days) and no cumulative toxicity has been noticed. Neutropenia can require temporary dose adjustment.

Significant anemia (grade>2) complicates 2% of cycles.

Thrombocytopenia has been observed only in pre-treated patients (1,2% of cycles).

Hematological side effects, although the dose-limiting ones, have rarely been severe : however impaired marrow function can increase both their incidence and severity and can require dose-reduction of navelbine.

- *Non hematological side effects.* Neurotoxicity manifested by a reduction of osteo-tendinous reflexes (6-29% of patients) and/or constipation (0-17% of patients) remains a rare event. Paresthesias occur in less than 2% of patients. Duration of treatment with navelbine, prior therapy with neurotoxic agents, abdominal irradiation can increase incidence of those side effects.

Nausea and vomiting occur in 3% of patients receiving navelbine. Here again previous therapy with emetogenic agents and/or abdominal irradiation can increase incidence of this side effect. Control of drug-induced emesis has never been a problem along those phase II studies.

Significant alopecia (grade >2) has been observed in 6% of patients. It can be easily prevented by scalp refrigeration.

No other side effects have been observed.

## Conclusions

Although still at an early stage of its development, Navelbine® has deserved an unusual amount of researches.

Beginning with an original modification of the basic structure of vinca alkaloids, this has lead to a compound with specific pharmacological properties, not only compared to that of other VA but more generally in the field of anticancer agents. Available data demonstrate not only a broad spectrum of activity but also side effects limited to neutropenia, thus establishing promising therapeutic index in animals and in humans. Navelbine may well be one of the more active agents in non small cell lung cancer and breast cancer. Further studies should establish the role of navelbine and define optimal combinations in those indications and investigate activity and safety in other tumor types.

Simultaneously, the specific approaches used to study Navelbine have brought new knowledge about the class of Vinca alkaloid agents : the study of reconstituted microtubular systems supplies tools for the screening of the antitumor activity and of the neurological toxicity; pharmacokinetics have unequivocally shown liver metabolism of VA and the possibility for entero-hepatic recirculation. These are some examples to show to which extent study of navelbine has increased the bulk of knowledge on vinca alkaloids.

Apart from ongoing studies, studies aiming to demonstrate bioavailability of navelbine given orally are in progress. Should they be successful that they would lead to further renewal of vinca alkaloids.

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